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THE GORDIAN KNOT OF REVASCULARIZATION FOR MULTIVESSEL CORONARY ARTERY DISEASE

To the Editor:

We read with great interest a recent meta-analysis by Yan and associates[1] of randomized and norandomized studies of percutaneous coronary intervention with drug-eluting stents (DESs) versus coronary artery bypass grafting (CABG) for coronary artery disease, including not only multivessel disease (MVD) but also single-vessel disease or left main coronary artery disease. This meta-analysis,[1] as well as a previous meta-analysis of MVD,[2] demonstrated no difference in all-cause mortality at least 1 year after DES and CABG treatments. Although these

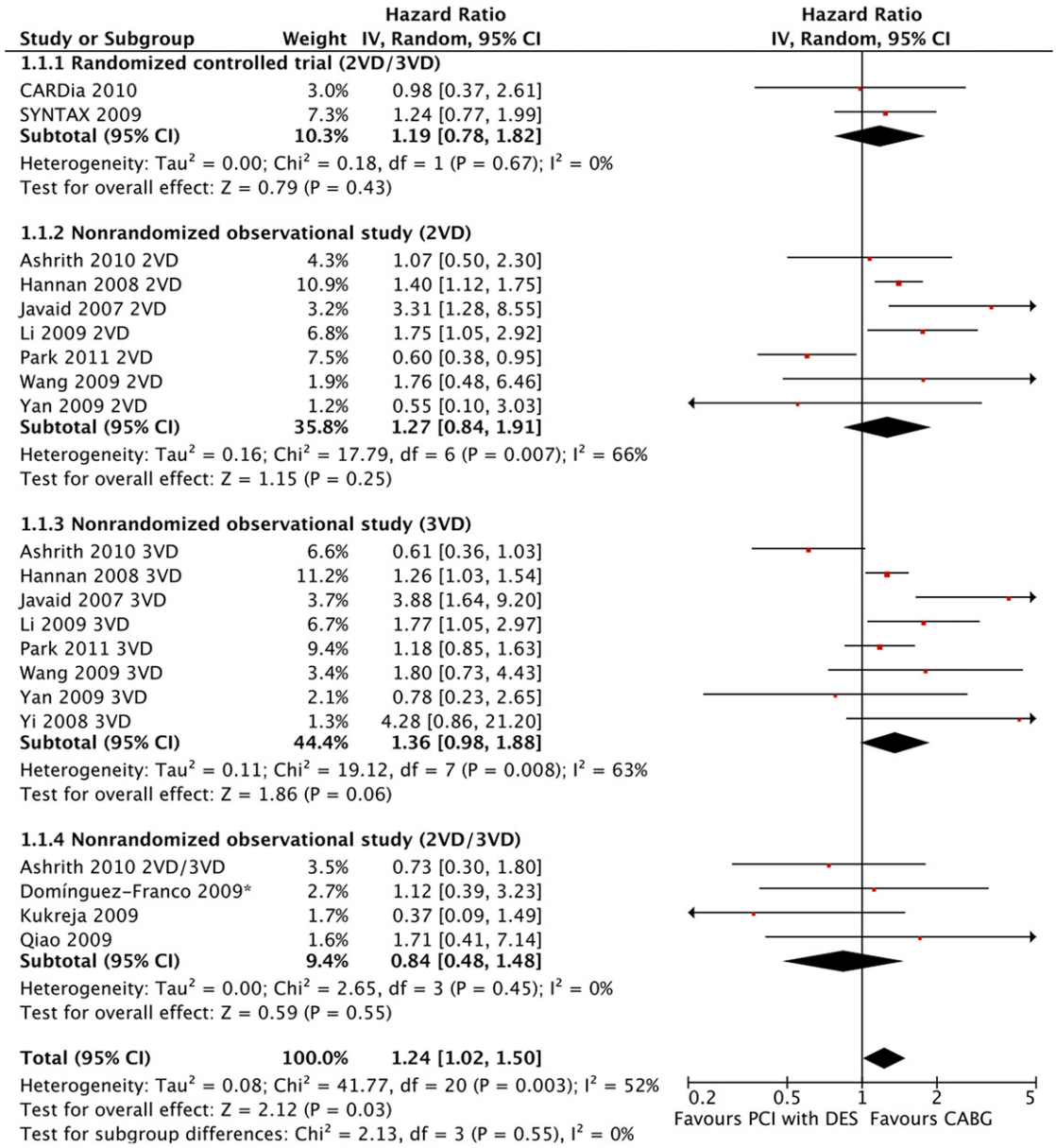

FIGURE 1. Follow-up (≥1 year) all-cause mortality among patients with multivessel disease assigned to percutaneous coronary intervention *(PCI)* with drug-eluting stent *(DES)* versus coronary artery bypass grafting *(CABG). Asterisk* indicates that the study provided an adjusted odds ratio. *IV,* Inverse variance; *CI,* confidence interval; *2VD,* double-vessel disease; *3VD,* triple-vessel disease; *CARDia*, Coronary Artery Revascularization in Diabetes trial[4]; *SYNTAX,* Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial.[5]

meta-analyses[1,2] included nonrandomized observational studies, data of unadjusted crude mortality were abstracted and combined. In contrast, our preliminary meta-analysis[3] of adjusted risk estimates from nonrandomized studies have suggested that DES use may increase mortality at 1 year or more relative to CABG for MVD. To assess whether DES treatment for MVD increases follow-up mortality relative to CABG, we updated our previous meta-analysis,[3] combining not unadjusted but adjusted risk estimates.

Studies considered for inclusion met the following criteria: the design was a comparative study (randomized controlled trial or nonrandomized observational study); the study population was limited to patients with MVD; patients were assigned to DES or CABG treatment; and main outcomes included adjusted (in case of observational studies) hazard ratios (HRs), or odds ratios if HRs were unavailable, for all-cause mortality at 1 year and beyond. Our comprehensive search (current through January 2011) identified 2 randomized trials[4,5] and 11 nonrandomized studies. We included 2 randomized trials (Coronary Artery Revascularization in Diabetes trial [CARDia][4] and Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial [SYNTAX][5]), although they included complex single-vessel disease (6.9%) and left main coronary artery disease without MVD (12.7%), respectively. We abstracted 2 unadjusted HRs from randomized trials and 18 adjusted HRs and 1 adjusted odds ratio from nonrandomized studies. Pooled analysis of all the 21 risk estimates demonstrated a statistically significant 24% increment in mortality with DES treatment relative to CABG in a random-effects model (HR, 1.24; 95% confidence interval, 1.02–1.50; $P = .03$; Figure 1). There was significant between-study heterogeneity ($P = .003$) but little difference in the pooled result from fixed-effects modeling (HR, 1.25; 95% confidence interval, 1.12–1.39; $P < .0001$). When 7 HRs in double-vessel disease and 8 HRs in triple-vessel disease were pooled separately, DES treatment was associated with, respectively, a statistically nonsignificant 27% and a 36% increment in mortality relative to CABG. Eliminating the 2 randomized trials[4,5] that included a few with single-vessel disease or left main coronary artery disease without MVD did not substantially change the pooled point estimate (random-effects HR, 1.25; 95% confidence interval, 1.005–1.55; $P = .045$). There was no evidence of significant publication bias ($P = .88$ by an adjusted rank-correlation test, $P = .96$ by a linear regression test).

Despite the results of the previous unadjusted meta-analyses, including that of Yan and collaborators,[1,2] we found our current adjusted meta-analysis of mainly nonrandomized observational studies with a few randomized controlled trials to indicate that DES treatment for MVD may increase all-cause mortality at 1 year and beyond by 24% relative to CABG. CABG rather than DES treatment should therefore be considered for MVD, because follow-up mortality reduction must imply the greatest clinical benefit among patients with MVD. To cut the Gordian knot of DES versus CABG for MVD, however, additional randomized trials are needed.

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Reply to the Editor:

We congratulate Takagi and colleagues on their updated meta-analysis comparing drug-eluting stent (DES) treatment with coronary artery bypass grafting (CABG) for patients with multivessel coronary artery disease. Our meta-analysis of trials (1 randomized, 24 nonrandomized) comparing CABG with DES treatment for multivessel coronary artery disease showed similar rates of all-cause mortality in the 2 groups but a lower incidence of major adverse cardiac and cerebrovascular events in the CABG group at 1 year and beyond.[1] The major contributor to the increased incidence of major adverse cardiac and cerebrovascular events seen in the DES group was the increased rate of repeat revascularization in that group.

Unlike our meta-analysis, in which unadjusted hazard ratios from the observational studies were used, Takagi and colleagues' analysis used adjusted hazard ratios to demonstrate significantly increased mortality in the DES group beyond 1 year. When trials including patients with 2-vessel disease and 3-vessel disease were pooled separately, no significant difference in mortality was seen.

These studies provide further evidence that CABG remains the standard of care for patients with multivessel coronary artery disease. In the 3-year outcomes of the Synergy